tween Big-ET and ET-1 antisera. In addition, staining for specific cell types, including macrophages (KP-1), endothelial cells (Factor VIII), and myointimal cells (actin), was performed. Eight primary native lesions, six restenotic lesions, and six vein graft (VG) lesions were studied. In all lesion types, intracellular Big-ET and ET-1 were present and in the extracellular matrix and colocalized to area with endothelial cells, macrophages, fibroblasts, and myointimal cells. ET-1 and Big-ET were colocalized to area with myointimal cells only in the primary native lesions. This study demonstrates the presence of Big-ET and ET-1 in coronary and VG atherosclerotic and restenotic lesions. This study suggests that ET is produced locally in the atherosclerotic and restenotic lesions by endothelial and nonendothelial cells. ET may play a role in the changes in tissue architecture and pathogenesis of coronary and VG atherosclerosis and restenosis.

1012-106 The Genotype of the ACE Gene and Collateral Formation

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The DD genotype of the angiotensin converting enzyme (ACE) gene has been reported to be a risk factor of myocardial infarction (MI), ischemic and idiopathic dilated cardiomyopathy, and left ventricular hypertrophy. The DD genotype of the ACE gene is associated with higher plasma ACE level, and thus may be associated with higher angiotensin II production in peripheral tissues. Because intimate involvement of angiotensin II in ventricular remodeling after MI has been reported, the genotype of the ACE could influence ventricular function after MI. The study population consisted of 66 subjects of MI who were performed twice coronary angiography (CAG) and left ventriculography(LVG). The first LVG was performed at 3.0 ± 2.9 months, and the second was performed at 10.2 ± 9.9 months from the onset of MI.

	ID + DD (n = 41)	II (n = 25)	P
EF 1st	0.568 ± 0.153	0.590 ± 0.116	0.547
EF 2nd	0.543 ± 0.133	0.623 ± 0.113	0.015
Collateral(+/−)	6/35	9/16	0.045

EF 2nd in subjects with either ID or DD genotype was significantly lower than in subjects with II genotype. Interestingly, presence of collateral circulation to infarct-related artery at the first CAG was more frequently observed in subjects with II genotype. To confirm the latter, we analyzed all subjects with ischemic heart disease who were performed CAG in our department in 1993.

	ID + DD (n = 91)	II (n = 67)	P
Female/Male	19/72	15/52	0.820
AP/OMI	21/70	23/44	0.119
RCA + Cx/LAD	37/54	34/33	0.208
TIMI(0-2/3)	51/40	38/29	0.932
Collateral(+/−)	28/63	36/31	0.003

Thus, presence of collateral circuletion was more frequent in subjects with II genotype. This study suggests that the ACE genotype may influence left ventricular function after MI through affecting collateral formation.

1012-107 Monocyte Chemotactic Protein-1 Expression in Smooth Muscle Cell Cultures Derived from Human Coronary Arteries

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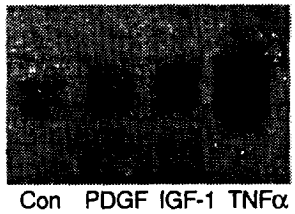
Peripheral blood monocytes and monocyte-derived macrophages are believed to play a pivotal role in the development of early atherosclerotic lesions. Excessive smooth muscle cell (SMC) proliferation leads to coronary restenosis after interventional procedures. We postulate that monocyte chemotactic protein-1 (MCP-1), by attracting monocytes to the site of vascular injury may indirectly augment this process. We also hypothesize that MCP-1 expression by human SMC may be mediated by cytokines and growth factors. Accordingly, we studied SMC cultures derived from tissue obtained by directional coronary atherectomy, evaluating MCP-1 expression by Northern blot analysis. Cells were grow in M-199 medium to over 95% confluence, for the last 24 hrs in serumless medium. MCP-1 expression was assessed in unstimulated (control) cells, and after 6 hrs stimulation with platelet derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1) and tumor necrosis factor alpha (TNF_α). Autoradiographs were developed, scanned and digitized using NIH 1.53b10 software. Our findings suggest that unstimulated human coronary SMC derived cultures express MCP-1 and furthermore this expression is markedly increased after stimulation with cytokines (by 21.4% after stimulation with PDGF, 30.3% after IGF-1 and 119.1% after TNF_α).



Conclusions: SMC cultures derived from human coronary samples obtained by DCA express MCP-1 during their quiescent phase, and this expression is markedly increased by the cytokines PDGF, IGF-1 and TNF_α. Thus by attracting monocytes to the area of vascular injury, MCP-1 may be intimately involved in coronary restenosis, playing an important role in the pathophysiology of this process.

1013 Peripheral Vascular Disease — Thrombosis

Wednesday, March 22, 1995, Noon–2:00 p.m.
Ernest N. Morial Convention Center, Hall E
Presentation Hour: 1:00 p.m.–2:00 p.m.

1013-68 Postoperative and Late Prognosis for Diabetics Undergoing Vascular Surgery: Combining Clinical Evaluation and Dipyridamole-Thallium Imaging Improves Risk Stratification

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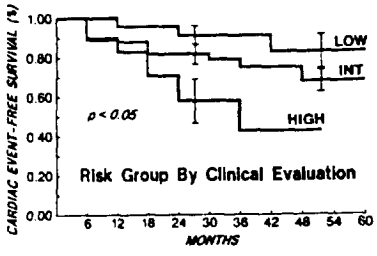
Prior studies suggest that pts with diabetes mellitus (DM) have a poor prognosis after vascular surgery and do not benefit from preoperative risk stratification by clinical evaluation or dipyridamole-thallium (DT) imaging because of a high prevalence of underlying coronary artery disease. To determine the postop and late prognosis for diabetics undergoing vascular surgery and the utility of clinical evaluation and DT for stratifying risk; we studied 122 pts with DM who underwent clinical evaluation and DT prior to vascular surgery. Based on the number of clinical markers present (using a previously described clinical risk index: prior MI, angina, Q wave on ECG, age > 70 yrs, CHF); pts were classified into low (0), intermediate (1–2), and high risk (>2 markers) for postop and late cardiac events. DT was assessed for reversible (REV) and fixed defects. There were 17 (14%) pts with postop events (4 cardiac deaths, 13 non-fatal MIs), and 23 (22%) with late events (8 cardiac deaths, 15 non-fatal MIs) on follow up which was possible in 98% of pts and was to 50 ± 5 months (75th quintile). On multivariate analysis, the only predictor for postop event was REV ($p < 0.01$) in this inherently high risk cohort. Successful risk stratification for late events was achieved by clinical index. DT was not of prognostic value for late event.



Conclusions: (1) Although diabetics are at high risk for events, dipyridamole-thallium imaging provides additional useful perioperative risk stratification. (2) The absence of clinical markers identifies a group with significantly better late cardiac event-free survival.

1013-69 Dipyridamole Rb-82 Positron Emission Tomography Has Limitations for Predicting Cardiac Events Peri- and Post-Operatively after Vascular Surgery

Kesavan Shan, Thomas Marwick, Raymundo Go, William MacIntyre, Donald Underwood, James Thomas. *Cleveland Clinic Foundation, Cleveland, OH*

Thallium imaging has been used to risk-stratify pts undergoing vascular surgery (VS), though the efficacy of this approach is debated. Positron emission tomography (PET) has the benefit of permitting a true resting scan, mea-

surement of the extent of ischemia, and is highly specific for the diagnosis of coronary disease.

We investigated the benefit of more accurate identification of ischemia and a lower frequency of false positives by using PET for risk stratification in 77 pts (68 ± 9 y, 52 males) undergoing VS (including 39 aortic operations — 51%) *without* recent myocardial revascularization. One or more clinical risk factors (age > 70, diabetes, angina, prior infarction or heart failure) were present in 63 pts; 32 had >2 factors. PET followed infusion of 60 mCi of Rb-82 at rest and after dipyridamole-handgrip stress. Using a quantitative color scale in a 24 segment model of the left ventricle, scans were reported as normal, fixed defects only (FD) or reversible (deterioration > 15% with stress) defects (RD). Events included infarction (MI) and unstable angina (UA), perioperatively and at late follow-up (17 ± 6 months) in 74 pts.

Fourteen pts (18%) suffered *peri-operative events* (5 MI, 9 UA, no cardiac deaths) giving PET-RD a sensitivity of 71%. Of 63 pts without events, RD was present in 16 (p = 0.003) giving a specificity of 66%. Seven pts suffered *late events;*

Rb-PET	Perioperative MI	Perioperative UA	Late events
RD (n = 26)	2	8	3
FD (n = 31)	1	0	4
Normal (n = 20)	2	1	0

Among 26 pts with RD (19 of whom were on anti-anginal therapy at the time of surgery), only 10 (38%) had perioperative events. The extent of ischemia in pts with RD having events (9 ± 7 segments) exceeded that in pts with RD not having events (6 ± 4 segments, p = NS). In pts with RD, 7/10 pts with events had extensive ischemia (>5 segments), compared with 9/16 without events (p = NS).

Conclusion. Absence of RD by PET confers a low probability of events (especially UA), comparable to conventional imaging. FD by PET are not associated with events. However, RD at PET has a low specificity for peri-operative events (irrespective of extent of RD); avoidance of events in the absence of myocardial revascularization may be attributable to medical and anesthetic measures.

1013-108 Is Persantine Thallium Scintigraphy Cost Effective and Reliable in the Preoperative Evaluation of Patients Referred for Peripheral Vascular Surgery?

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Asymptomatic CAD has been shown to be associated with a high risk of perioperative cardiac events in patients (pts) undergoing surgery for peripheral vascular disease (PVD). Dipyridamole thallium (SPECT) scintigraphy (DTS) is considered the most useful screening test for stratification of these pts. Comparative prospective evaluation of various noninvasive tests for detection of latent CAD in PVD pts is lacking. In this study, 100 consecutive patients referred for PVD surgery were evaluated by DTS, low work load exercise treadmill test (ETT) and ambulatory ECG monitoring (AEM). Pts with abnormal findings on any of the three noninvasive tests were evaluated with coronary angiography (angio) for further stratification. Fifty-five pts had reversible perfusion defects on DTS. Of the 55 + pts with DTS, 49 had data on AEM with 39% having evidence of ambulatory ischemia; 48 of the 55 pts performed ETT with ischemia induced in 13%. Of the 41 pts with normal DTS findings, 12 (29%) had ischemia during ETT (n = 6) or AEM (n = 6); 64% of these pts had multi-vessel CAD by angio. Statistical modeling and analysis of important clinical variables, AEM ischemia, and angio findings were compared with DTS for predicting CAD. These analyses revealed that family hx of CAD, chest pain, smoking, age ≥ 65 years, and ischemia on AEM were highly predictive of CAD with a positive predictive value of 89% and a specificity of 92%. These findings suggest that a careful evaluation of clinical parameters and AEM results can provide reliable and clinically meaningful data predictive of significant CAD in pts referred for PVD surgery.

Conclusion: Our data have demonstrated that the findings on DTS are not always reliable and its routine use might not be warranted in preoperative evaluation of patients with asymptomatic CAD referred for peripheral vascular surgery.

1013-109 Effect of Picotamide in Preventing Cardiovascular Events in 438 Diabetic Patients: Results of a Multi-Centre, Placebo Controlled, 18-Month Study

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In the A.D.E.P. (Atherosclerotic Disease Evolution by Picotamide) study 2,304 patients with peripheral obstructive arterial disease (POAD) were recruited for a double blind 18-month multi-centre trial comparing picotamide (300 mg t.i.d.), an antiplatelet drug which inhibits thromboxane A2 (TxA2) synthase and antagonizes TxA2 receptor, and placebo. In the study population as a whole, 151 events (13.1%) occurred on placebo and 122 (10.6%) on picotamide, with a relative risk reduction of 19%, (p = 0.056, Logrank test, intention to treat analysis). The effect of picotamide was assessed in the A.D.E.P. subgroup of diabetic patients, in order to test if the drug was still effective in patients at higher risk of cardiovascular complications. Diabetic patients were 438 (230 on picotamide and 208 on placebo). Most of them were male (80%), with a mean age of 64 years (min 40, max 75). Six per cent were insulin-dependent. The main risk factors (smoking, hypertension, previous vascular surgery, ankle/arm pressure ratio, WBC count and fibrinogen) were similarly distributed in the two groups.

Diabetic POAD patients on placebo suffered from a total of 33 cardiovascular events (12 major and 21 minor) (15.9%), whereas those on picotamide suffered from a total of 20 events (6 major and 14 minor) (8.7%) (relative reduction of risk: 45.2%, p = 0.022 at Logrank test, intention to treat analysis). Both major and minor events occurred more frequently in the placebo than in the picotamide group. The overall incidence of major events was 5.8% on placebo and 2.6% on picotamide (relative risk reduction of 59.8%). Death occurred in 6 patients on placebo (2.9%) and in 3 on picotamide (1.3%). Non fatal major events (stroke, myocardial infarction and amputation) were 6 on placebo and 3 on picotamide. Minor events were 10.1% on placebo and 6.1% on picotamide (relative risk reduction of 39.8%). Adverse reaction, mainly gastrointestinal, occurred in 16% of patients, regardless of the treatment.

In conclusion, this analysis indicates that Picotamide significantly reduces cardiovascular events in diabetic POAD patients, suggesting its potential use in patients at high risk of atherosclerotic progression.

1013-110 Effects of Cocaine on Human Platelet Aggregation In Vivo

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A temporal relation has been established between cocaine ingestion and acute myocardial infarction. Based on in vitro data, an increase in platelet aggregation has been hypothesized as a factor contributing to ischemic events following cocaine abuse. To determine whether cocaine administration increases platelet aggregation in vivo, 12 healthy volunteers were studied twice, each subject receiving cocaine (2 mg/kg intranasally) or placebo in a double-blind, randomized, crossover fashion. Aggregation was tested at baseline and 40, 80 and 120 minutes following administration of the study drug, using a turbidimetric method. Aggregation was induced using arachidonic acid (AA, 625 μM), epinephrine (5, 10 and 25 μM), and ADP (1, 2, 4 and 10 μM). Data are expressed as difference in aggregation (%) [cocaine - placebo]:

Agonist	(μM)	Baseline	40 min	80 min	120 min
ADP	1	0 ± 1	0 ± 1	−2 ± 1	−2 ± 2
	2	1 ± 3	0 ± 2	−4 ± 2	−5 ± 3
	4	6 ± 5	−2 ± 5	−6 ± 6	−10 ± 8
	10	4 ± 3	−1 ± 3	−1 ± 3	−8 ± 3
Epinephrine	5	2 ± 9	0 ± 9	−4 ± 6	−11 ± 7
	10	−6 ± 7	−6 ± 4	−5 ± 4	−11 ± 7
	25	3 ± 6	−3 ± 4	−5 ± 6	−13 ± 6
AA	625	11 ± 8	3 ± 12	−3 ± 11	−2 ± 14

Data are presented as mean ± SEM. By doubly repeated ANOVA, there was a decrease in aggregation after cocaine no matter which of these 3 agonists were used (p < 0.05).

Conclusions: These data do not support an increase in platelet aggregation as a primary cause of myocardial infarction following low dose cocaine administration. It is unlikely that low dose cocaine causes a direct thrombogenic effect. No conclusion can be reached for high dose cocaine.

1013-111 Mechanisms Underlying the Morning Increase in Platelet Activation: Study of Whole Blood Platelet Flow Cytometry

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Introduction: Immediately after arising in the morning there is an increase in the incidence of acute myocardial infarction, stroke and sudden death. Upon assumption of the upright posture platelet aggregation, as measured by conventional techniques using platelet rich plasma, occurs more readily in response to standard aggregating agents. Whether platelet aggregability in the physiological milieu of whole blood also increases and whether this increase in platelet aggregability is also accompanied by activation-dependent